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eFiled Application Information

EFS ID	3855192
Application Number	11642029
Confirmation Number	8909
Title	Control of CCI-779 dosage form stability through control of drug substance impurities
First Named Inventor	Joseph Thomas Rubino
Customer Number or Correspondence Address	38199
Filed By	Cathy A. Kodroff/Lynn Brown-Fischer
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Application Details

Submitted Files	Page Count	Document Description	File Size	Warnings
am102119response.pdf	6		236458 bytes	PASS

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AM-102119

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appln. No. 11/642,029 Confirmation No.: 8909

Applicant: Rubino

Filed: December 19, 2006

TC/A.U.: 1614

Examiner: Thomas, Timothy P.

Customer No: 38199

Title: CONTROL OF CCI-779 DOSAGE FORM STABILITY THROUGH CONTROL OF DRUG SUBSTANCE IMPURITIES

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

RESPONSE

Sir:

This paper is in timely response to an Office Action dated May 29, 2008. Kindly amend the application as follows.

The **Amendment** of the claims begins on page 2.

The **Remarks** begin on page 5.

AMENDMENTS TO THE CLAIMS

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

1 (Currently Amended). A method of decreasing the rate of oxidative degradation of ~~preparing~~ a rapamycin composition ~~having increased potency~~, said method comprising the steps of:

selecting a rapamycin compound having less than 1.5% oxidative and hydrolytic rapamycin impurities; and

formulating the selected rapamycin with an antioxidant in an amount of about 0.075 wt% to about 0.5% and optional excipients.

2 (Original). The method according to claim 1, wherein the selecting step comprises screening the rapamycin in a high performance liquid chromatography assay.

3 (Original). The method according to claim 1, wherein the antioxidant is selected from the group consisting of a tocopherol, vitamin C, 2,6-di-tert-butyl-4-methylphenol, and mixtures thereof.

4 (Original). The method according to claim 3, wherein the antioxidant is α-tocopherol.

5 (Original). The method according to claim 1, wherein the selected rapamycin has less than 0.5% oxidative impurities.

6 (Original). The method according to claim 1, wherein the selected rapamycin is formulated for parenteral delivery.

7 (Original). The method according to claim 1, wherein the selected rapamycin is formulated as a liquid concentrate.

8 (Original). The method according to claim 7, wherein the selected rapamycin is formulated with d,l-α-tocopherol, anhydrous citric acid, dehydrated alcohol, and propylene glycol.

9 (Original). The method according to claim 1, wherein the selected rapamycin is formulated for oral delivery.

10 (Withdrawn – Currently Amended). A method of decreasing the rate of oxidative degradation of ~~preparing~~ a rapamycin composition ~~having increased potency~~, said method comprising the steps of:

selecting a rapamycin compound having less than 1.5% oxidative and hydrolytic rapamycin impurities;

formulating the selected rapamycin with at least two antioxidants in an amount of about 0.075 wt% to about 0.5% and optional excipients.

11 (Withdrawn). The method according to claim 10, wherein at least one of the antioxidants is vitamin C or 2,6-di-tert-butyl-4-methylphenol.

12 (Withdrawn). The method according to claim 10, wherein said at least two antioxidants are vitamin C and 2,6-di-tert-butyl-4-methylphenol.

13 (Withdrawn). The method according to claim 1, wherein said rapamycin is selected from the group consisting of rapamycin and CCI-779.

14 (New). The method according to claim 1, wherein the antioxidant is present in an amount of about 0.075% to about 0.2%.

15 (New). The method according to claim 1, wherein the antioxidant is present in an amount of about 0.075%.

16 (New). The method according to claim 1, wherein the rapamycin compound degrades less than about 2% after storage for 3 to 5 months at 25°C or one month at 40°C.

17 (New). The method according to claim 1, wherein the rapamycin compound degrades less than about 1% after storage for 3 to 5 months at 25°C or one month at 40°C.

REMARKS/ARGUMENTS

Claims 1-17 are pending. Claims 10-13 are withdrawn as being drawn to a non-elected species. Rejoinder of these claims is requested should a generic or linking claim be found allowable.

The amendment to claim 1, claim 10 and new claims 14 -17 are supported, e.g., on page 6, lines 22-25; page 8, lines 11 – 13 and page 21, line 10, and throughout the specification. No new matter is added by this amendment.

The amendment to claim 1 renders the rejection of claims 1-9 as being indefinite for reciting the term "increased potency" moot. Withdrawal of this rejection is requested.

> *Claims 1 and 3-9 are rejected as anticipated by under 35 USC 102(b), or in the alternative, as obvious under 35 USC 103(a) over Rubino et al, WO 2004/011000. The examiner has taken the position that the present method is inherently disclosed in the AM100802 application, which describes parenteral formulations which require alcohol co-solvents and either an antioxidant or a chelating agent.*

Applicants respectfully traverse this rejection.

Crucial to the present invention is the inventor's recognition that there is a threshold amount of CCI-779 impurities below which an anti-oxidant functions more effectively to control the rate of oxidative degradation. As first appreciated by the inventor, anti-oxidants are significantly more effective at inhibiting the growth (rate) of oxidative impurities in a CCI-779 formulation, if the starting amount of impurities is lower than 1.5%. There is nothing in the cited prior art which suggests that the effectiveness of an anti-oxidant in reducing the rate of oxidative degradation of a rapamycin is related to the amount of impurities present in the initial composition.

For this reason, the method of the invention is novel and nonobvious.

The examiner further argues that it would have been obvious to select CCI-779 having less than 1.5% oxidative and hydrolytic rapamycin impurities for formulation with the present invention. However, while Rubino provides a formulation containing either an antioxidant or a chelating agent, there is no recognition of *the method* of the

present invention. Further, the present invention does not require the co-solvent which is a requirement of Rubino.

Reconsideration and withdrawal of this amendment is requested.

Claim 2 is further rejected on the combination of Rubino et al, in combination with Oellerich et al, Clin Biochem, 37, 424-428 (2004), which is relied upon for teaching determining blood levels of sirolimus by HPLC.

Applicant respectfully traverses this rejection.

Neither Rubino alone, or in combination with Oellerich, teaches or suggests the effectiveness of an anti-oxidant in reducing the rate of oxidative degradation of a rapamycin is related properties to the amount of impurities present in the initial composition. Therefore, there is no suggestion that the rate of growth of oxidative degradation is related to selection of a rapamycin composition having lower than the recited amount of such impurities.

Reconsideration and withdrawal of this amendment is requested.

The Director is hereby authorized to charge any deficiency in any fees due with the filing of this paper or during the pendency of this application to Deposit Account Number 08-3040.

Respectfully submitted,
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